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Correspondence

TO THE EDITOR, *British Journal of Venereal Diseases*

Penicillinase-producing *Neisseria gonorrhoea* in Jakarta, Indonesia

Sir,

Between 30 April 1981 and 30 April 1982, 156 cases of gonorrhoea were confirmed by culture in the department of microbiology of the Medical Faculty, University of Indonesia. Of these cases, 39 were due to infection with penicillinase-producing *Neisseria gonorrhoeae* (PPNG). No PPNG strains had been detected in this department before April 1981. All 156 cases occurred in Indonesian patients, both male and female. The first impression was that men seemed to be more affected by PPNG infections than women (table I). Statistically the difference was not significant at the 1% level ($\chi^2 = 0{\cdot}42$, $P < 0{\cdot}5$). Does this imply that men and women run a similar risk of developing PPNG infections?

Isolation and identification of PPNG and non-PPNG strains were carried out according to standard methods. The minimum inhibitory concentration of penicillin was measured by a plate dilution method. All PPNG strains showed resistance to 128 μg/ml penicillin G. Further testing of higher concentrations of penicillin could not be performed since these 39 PPNG strains did not remain viable. Several PPNG strains collected later (after April 1982) were tested at higher concentrations of penicillin (table II); none of the 14 PPNG strains showed any inhibition of growth on 10-unit penicillin discs.

Yours faithfully,

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TABLE I *Number of PPNG infections diagnosed between 30 April 1981 and 30 April 1982*

Patients' sex	*PPNG strains*	*Non-PPNG strains*	*Total No of cases*
Male	37	105	142
Female	2	12	14
Total	39	117	156

TABLE II *Minimum inhibitory concentrations (MICs) of penicillin for 14 PPNG strains*

	MIC of penicillin (μg/ml):				
	128	*256*	*1024*	*2048*	*4096*
PPNG Strains	3	1	1	1	8

TO THE EDITOR, *British Journal of Venereal Diseases*

Changes in intravascular kininogen during the Jarisch-Herxheimer reaction in secondary syphilis

Sir,

The pathogenesis of the Jarisch-Herxheimer reaction (JHR) after the treatment of syphilis remains obscure. It has been attributed to the release of treponemal breakdown products and release of endogenous leucocyte pyrogen[1] after the administration of treponemicidal drugs. Loveday[2] and others[3] have reported falls in early components of the classical pathway of the complement system which paralleled the severity of the preceding JHR. These workers proposed a scheme for the mode of activation of complement, kinin formation, and other inflammatory mediators and their possible relation to the clinical features of the JHR. We report changes in intravascular kininogen in six patients with early secondary syphilis and in one control subject in the first eight hours after the initial therapeutic dose of antibiotics.

Six seropositive patients (aged 26-66 years) with secondary syphilis who had a typical rash and minimal or no lymphadenopathy were studied. After being given 600 000 units of procaine penicillin (Distaquine suspension) by intramuscular injection they were observed for at least eight hours. Before treatment pulse, blood pressure, temperature, and clinical features were recorded and blood samples taken. Treatment was given and observations repeated and specimens taken at ½, 1, 1½, 2, 3, 4, 6, and 8 hours. Each blood sample was heparinised (100 U heparin/10 ml blood) avoiding contact with glass, and the plasma was separated within 30 minutes and frozen at −70°C.

Assay of plasma kininogen was expressed as bradykinin in μmol/l released from plasma kininogen by trypsin. The kinin released was assayed on the isolated rat uterus.[4] Immunoglobulin assays for IgG, IgM, and IgA were carried out using standard Hyland Immunoplates; results were expressed as percentages of those pooled for normal human serum.

The six patients showed varying degrees of clinical change after the start of treatment. In case 1 the patient had a severe JHR; the rash increased in intensity and the temperature rose to 38·8°C and the pulse rate to 100/minute; a slight fall in pulse rate produced a subsequent rise in blood pressure. This patient developed rigors, and observations and collection of blood samples were stopped at the six-hour interval. In case 2 the patient had a similar reaction with an increase in the intensity of the rash, a rise in temperature to 38·8°C, an increase in pulse rate to 110/minute, and a similar but more pronounced change in blood pressure than in case 1. Both these patients reported severe symptoms

including myalgia, arthralgia, anorexia, and nausea. In cases 3 and 4 the patients had less severe reactions with rises in temperature to 38·9°C and 38°C respectively and an increase in pulse rate to 100/minute. Both patients showed a slight rash potentiation and felt nauseated and unwell for short periods. In cases 5 and 6 and the control subject 7 no reactions either objective or subjective occurred. When they did occur reactions began three to four hours after initiation of treatment.

A fall in intravascular kininogen occurred in several patients. This fall was most pronounced in the patients in cases 1 and 2 who had severe JHRs (figure). In case 1 the patient had a fall in intravascular kininogen of 60% (from 5·2 to 2·1 μmol equivalents of bradykinin/litre of plasma), the maximum occurring between the 1½- and three-hour intervals; in case 2 the patient had a fall of 96% (from 2·85 to 0·18 μmol equivalents of bradykinin/litre of plasma), the maximum occurring between the one- and three-hour intervals. In both patients values returned to normal by the six-hour interval. In cases 3 and 4 the patients had a less pronounced fall in kininogen of 16% and 23% respectively, which was shorter in duration. No fall in intravascular kininogen occurred in cases 5 and 6 or in the control subject 7. The intravascular concentrations of IgG, IgM, and IgA rose slightly over the first four hours in cases 1 and 2; in cases 3 and 4 and the control subject 7 no overall changes occurred during the period of observation.

The JHR in the patients studied was associated with an early reduction in intravascular kininogen values, reflecting pronounced kinin formation. The degree of this change in individual patients paralleled the severity of the reaction and we propose that kinin may play a part in the pathogenesis of the JHR. It is unlikely that falls in kininogen values are due to non-specific extravasation of plasma proteins or transient haemodilution, since during this time the concentrations of three major classes of immunoglobulins tended to rise or remain steady.

Depletion of prekallikerein, an intermediate enzyme precursor in the plasma kinin forming system, and other protein mediators in *Borellia recurrentis* infection has been shown during the JHR two hours after treatment; these values returned to normal in the convalescent period.[5] Other workers[6] failed to show plasma kinin formation during the JHR in secondary syphilis but they omitted to take blood samples before the three-hour interval.

The scheme proposed by Loveday[2] and others[3] suggested several possible sites of kinin formation during the JHR: via immune complexes, Hageman factor, early complement components, and lysozymal enzymes. Kinins so formed would have biological properties to mediate, at least in part, the subsequent reaction. In addition they proposed that the main site of the JHR in syphilis was extravascular. This may explain why only the patients having severe reactions (and pronounced activation of kininogen) showed significant changes in kininogen in the intravascular compartment. The rapid return to normal values after 3-4 hours may not reflect cessation of activation but merely an increase in overall synthesis.

Further work is in progress to clarify the role of plasma enzyme systems in the pathogenesis of the JHR.

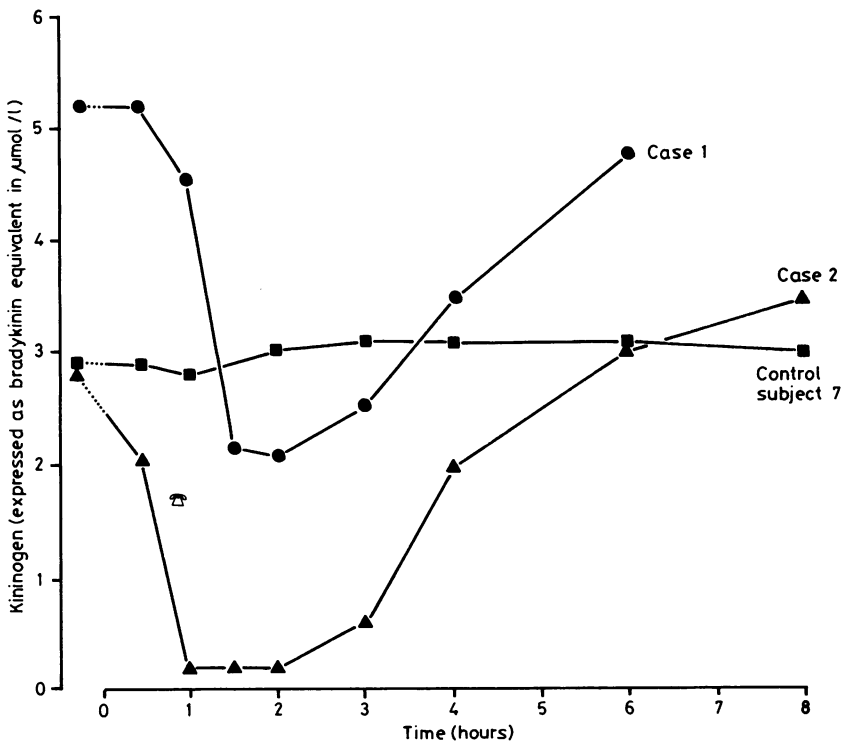

FIGURE Kininogen changes in cases 1 (●) and 2 (▲) and in the control subject 7 (■). In the two patients who had severe JHR maximum falls in intravascular kininogen occurred at one and two hours after treatment. No change was observed in the control subject.

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